

DETECTION OF URINARY TRACT OBSTRUCTION BY NERVE GROWTH FACTOR MEASUREMENT IN URINE

BACKGROUND OF THE INVENTION

1. Field of the Invention

The invention relates to the isolation of markers in urine to indicate the presence of irritative and/or obstructive conditions in the bladder. Additionally, the use of Ca^{++} -channel blockers is disclosed to inhibit the production of NGF and nerve growth.

2. Brief Description of the Prior Art

Historically, there has been a progression from anatomical to functional studies for the diagnosis of upper and lower urinary tract obstruction. However, these studies fail to predict ultimate changes in bladder or kidney function. For example, with obstruction of the lower urinary tract, urodynamic studies often do not correlate with the severity of symptoms and fail to demonstrate capacity for return to normal function following relief of obstruction.

Two major classes of voiding disorder in males and females are benign prostatic hyperplasia (BPH) and interstitial cystitis (IC). These cause, respectively, irritative/obstructive symptomology and idiopathic bladder and pelvic pain with voiding. An accumulating body of information links these conditions to changes in bladder innervation and that these may be orchestrated by neurotrophic factors.

Interstitial cystitis (IC) is an enigmatic disorder associated with chronic inflammation, whose primary manifestations are bladder pain and irritative voiding. IC affects up to 90,000 individuals and may be a heterogeneous syndrome yet therapy for this disease is inadequate. Since IC does not lead to life threatening problems such as renal insufficiency, infection or hemorrhage, a reasonable approach to therapy is to alleviate symptoms. However, lack of knowledge of the underlying pathophysiological cause(s) for this disorder has hampered the design of rational interventions. Because the cardinal symptoms of IC are bladder pain, urinary urgency or frequency not associated with involuntary bladder contractions, it can be assumed that activation of nociceptive afferents and/or pathways occur in IC. Nociceptive (pain) afferents and pathways are the specific and separate neural substrates for pain. Thus, a chronic pain disorder implies an alteration in the function of the nociceptive system.

Research on IC has been primarily focused on immunologic processes and urothelial permeability. However, inflammatory mediators and other second messengers alter bladder nerve activity and change production of growth factors including those trophic for nerves. Products released by inflammatory cells such as mast cells and lymphocytes, or alterations in urothelial permeability, may result in structural and functional changes in the bladder afferents and sensory pathways, including the nociceptive elements. There is no non-invasive diagnostic test available to determine whether a patient has IC.

Benign prostatic hyperplasia (BPH) is a disease in men characterized histologically by the formation of non-malignant prostatic nodules, and clinically by signs and symptoms of urinary obstruction produced by this abnormal growth. BPH accounts for an estimated 1.7 million physician office visits and nearly 400,000 prostatectomies in the United States and is the most common cause of major surgery in men over age 55. Despite the high prevalence and social impact of BPH, very little is known regarding the pathogenesis of symptoms accompanying outlet obstruction of the

bladder. This is especially relevant since symptoms and subjective clinical findings are the primary indications for intervention in BPH. Irritative symptoms, including urinary urgency, frequency and nocturia, are closely correlated with the need for intervention and have the greatest negative impact on the patients' quality of life. Additionally, BPH can cause an infravesical obstruction, and consequent damage to the detrusor muscle, even in the absence of troublesome symptoms and without a demonstrably enlarged prostate gland. Conversely, BPH, even with significant prostatic enlargement, does not always result in functionally obstructed voiding.

The degree of BPH has been assessed by estimating prostate size on a digital rectal exam. However, the degree of obstruction is not correlated with prostate size, probably due in part to location and the minimal involvement of the whole gland in infravesical obstruction. This indicates overall prostate size alone has poor sensitivity and specificity for the important symptoms of BPH.

Combined pressure/flow studies have been used to document obstruction of the bladder but this invasive test is expensive and requires special expertise and thus is a poor routine screening tool. A voiding flow rate offers a less invasive method of inferring obstruction, but this also suffers from poor specificity and sensitivity for obstruction. Despite these limitations, flow rate is used in the diagnosis, management and outcome analysis of BPH. Recently, a symptom index has been developed for BPH capable of discriminating between BPH and control subjects. This AUA International Prostate Symptom Score (I-PSS) has been shown to be internally consistent and to have excellent test-retest reliability. This self-administered questionnaire serves as an established and validated means of capturing the symptom severity of BPH. Questionnaire features and its performance suggest it is useful for discriminative, predictive and evaluative purposes. The I-PSS is not recommended to screen for BPH, but rather to assess symptom severity. The I-PSS may also be useful, with minor modification, for measuring severity of symptoms of other lower urinary tract disorders such as interstitial cystitis.

Further insight into the functional and structural consequences that accompany BPH has been obtained via transabdominal ultrasound of the bladder. This imaging method has been used to measure residual urine volume, estimate bladder wall thickness, indicate the extent of trabeculation and to help exclude other pathologies such as hydronephrosis, tumor and bladder stones in a minimally invasive manner.

In addition to IC and BPH, pain or discomfort is produced by other causes of bladder inflammation which include bacterial and parasitic infections, calculi, foreign bodies such as catheters, trauma, neoplasm, radiation therapy and chemotherapy. Some middle aged women suffer from an irritative voiding disease similar to BPH in men. Patients with inflammatory disorders often report that symptoms are affected by dietary substances, suggesting a direct effect of bladder contents on nerve activity or a functional alteration in afferents. IC patients report that the disease has a very uneven clinical course. Periods of intense pain and irritative voiding are interspersed with extended periods of time of relative freedom from symptoms. However, efforts to detect specific substances in the urine that reflect active or inactive phases of the disease, or that have diagnostic utility, have not met with success. No useful, protective or palliative dietary regimen has been discovered.

A diagnostic test would be useful to indicate for whom intervention is necessary and effective before irreversible